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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,018	10/12/2000	Philip Gotwals	A018	6239

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Biogen Inc  
14 Cambridge Center  
Cambridge, MA 02142

EXAMINER

ANDRES, JANET L

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/423,018	GOTWALS ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Janet L. Andres	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 February 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 8,9 and 11-21 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 5 is/are allowed.
- 6) ☒ Claim(s) 1-4, 6, 7, 10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

RESPONSE TO AMENDMENT

1. Applicant's amendment filed 5 February 2003 is acknowledged. Claims 1-21 are pending in this application; claims 8, 9, and 11-21 are withdrawn from consideration as being drawn to a non-elected invention. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

*Objections Withdrawn*

2. The objection to the specification is withdrawn in response to Applicant's amendment.

*Claim Rejections Maintained*

3. The rejection of claims 1-3 and 10 under 35 U.S.C. 112, first paragraph, as lacking enablement commensurate with the scope of the claims is maintained for reasons of record in the office action of paper no. 16.

Applicant argues that the specification provides guidance as to the variants that fall within the scope of the claims. Applicant argues that the specification discloses that the invention encompasses variants of the type II receptor. Applicant had provided a declaration under 37 C.F.R. 1.132 stating that one of skill could readily make variants of the type II receptors, and stating that *Massague* does not teach away from fusion proteins. Applicant further argues that the "key inquiry" is whether one of skill could identify, make, and test the proteins falling within the limitations of the claims. Applicant additionally states that the specification indicates the nature of the fusion partners. Applicant argues that the Lin patent suggests "a common functionality" between type I and II receptors.

Applicant's arguments and declaration have been fully considered but have not been found to be persuasive. Claims 1 and 10 are not limited to molecules of defined homology to

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TGF $\beta$ RII. They encompass all TGF $\beta$  receptors without limitation or exclusion, including those not yet known in the art. What one of skill in the art could make and use, based on Applicant's disclosure and Applicant's declaration, are variants of the TGF $\beta$  type II receptor. The specification provides no definition limiting "TGF $\beta$  receptor" to variants of the type II receptor. Applicant's specification indicates only that variants of the TGF $\beta$  type II receptor are encompassed by the invention. Nothing is excluded. Further, to define "TGF $\beta$  receptor" as claimed in claims 1 and 10 to mean "TGF $\beta$  type II receptor" would not be consistent with the terminology accepted by the art, which considers at least the type I receptors to be TGF  $\beta$  receptors. As stated in the office action of paper no. 14, *Massague* teaches that not all receptors bind TGF- $\beta$  independently. The section of *Lin* cited by Applicant teaches only that both types may be involved in signaling; there is no teaching to contradict the later teachings of *Massague* that they do not function in the same way.

Claims 2 and 3 are limited to type II receptors. However, they are not limited to the type of TGF-  $\beta$  bound. As stated in the office action of paper no. 14, one of skill in the art would not expect, based on the teachings of the art, that the type II receptor could be used to bind all TGFs  $\beta$  sufficient to inhibit their binding to other receptors. Applicant has not addressed this basis of the rejection and it is maintained for reasons of record in the previous office action.

Applicant argues that *Massague* does not teach away from the use of fusion partners, That *Massague* does not teach that fusion partners could affect binding does not serve to enable the invention as broadly claimed; the instant specification does not provide guidance as to how one of skill in the art would determine which ones would work. That the declaration and Applicant's specification address immunoglobulins does not serve as guidance for the invention

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as broadly claimed; all fusion molecules, not merely immunoglobulins, are within the scope of claims 1,2 and 10.

Thus one of skill in the art would not, based on the teachings of the art, expect to be able to use Applicant's invention as broadly claimed. Applicant's specification, which is directed to the type II receptors and variants thereof, does not provide compensatory teaching. What is provided is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Such an invitation is not sufficient guidance to allow one of skill to make and use the invention as broadly claimed with an expectation of success.

4. The rejection of claims 1-4, 6, 7, and 10 under 35 U.S.C. 103(a) is maintained for reasons of record in the office action of paper no. 14.

Applicant argues that neither *Lin* nor *Jacobs* provides showing to prepare fusion proteins as set forth in Applicant's specification. Applicant argues that, in light of the rejection of the claims as lacking enablement, the rejection of the claims under 35 U.S.C. 103 relies on impermissible hindsight. Applicant has provided a declaration under 37 C.F.R. 1.132 indicating that *Jacobs* provides no suggestion that TNF-R is analogous to TGF- $\beta$ -R, and that *Lin* teaches both agonism and antagonism.

Applicant's arguments have been fully considered but have not been found to be persuasive. As stated above, Applicant's claims encompass more than the particular variants set forth in Applicant's specification. Thus *Lin* and *Jacobs* need not make obvious precisely what Applicant has taught, but rather an invention within the scope of Applicant's claims. Similarly, claims 1-4, 6, 7, and 10 were rejected as lacking enablement commensurate in scope with the claims. That one combination within said scope is enabled does not serve to enable the invention

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as a whole for the reasons set forth above. No hindsight reasoning is required. That neither *Jacob* nor *Lin* individually teaches a fusion protein between TGF- $\beta$  type II R and Fc does not serve to render this embodiment of Applicant's claimed invention unobvious. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant states in the declaration under 37 C.F.R. 1.132 that *Lin* teaches both agonistic and antagonistic activity. However, while the claims of *Lin* generally encompass "modulation" by a soluble type II receptor, which could be either activation or inhibition, one of ordinary skill in the art would expect that the ligand would bind to the soluble receptor, and that as a consequence its binding to the cell surface receptor would be inhibited. Thus one of ordinary skill would expect, absent teachings to the contrary, that the "modulation" would be inhibitory. *Lin* also teaches that there are diseases that involve TGF- $\beta$  overproduction in column 9, lines 54-58. Thus one of ordinary skill would know from the teachings of *Lin* that there were conditions in which inhibition of TGF- $\beta$  binding to its receptors on the cell surface would be desirable, and would expect to be able to use the soluble type II receptor to this end. *Jacobs* teaches that another cytokine receptor, TNF- $\alpha$  R, similarly functions as an inhibitor and teaches that fusion with Fc improves this function. This improvement is not related to the structure of the receptor itself. *Jacobs* teaches that the advantage is due to bivalency: see column 7, lines 43-57. Thus one of ordinary skill in the art would expect a similar advantage from a similar fusion using the TGF- $\beta$  type II receptor. Thus, it would be obvious to one of ordinary skill in the art on reading

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the teachings of *Lin* and of *Jacobs* to generate a soluble TGF- $\beta$  type II receptor/Fc fusion product because one of ordinary skill would expect such a product to be useful to inhibit TGF- $\beta$ .

***Allowable Subject Matter***

5. Claim 5 is allowed over the prior art because *Lin* does not teach the rabbit sequence of instant SEQ ID NO: 8.

CLAIMS 1-4, 6, 7, AND 10 ARE REJECTED. CLAIM 5 IS ALLOWED.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 872-9306 or (703) 872-9307 for after final communications.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.  
April 15, 2003

  
YVONNE EYLER, PH.D.  
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